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10/540,215	06/20/2005	Gerolf Zimmermann	00401P0004WOUS	5244

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,215	ZIMMERMANN ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-39 and 41-62* is/are pending in the application.

4a) Of the above claim(s) *32-39 and 43-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31, 41-42 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Amendment filed on November 10, 2008 is acknowledged. Applicant has withdrawn claims 32-39, 43-61; cancelled claim 40; added new claim 62. Currently claims 31, 41-42 and 62 are active and will be examined in this action.

2. Amendment filed on November 10, 2008 is not compliant with 37 CFR 1.126. Applicant has cancelled claims 1-30, they should be listed as such in the amendment filed. The numbering of claims in the amendment filed on November 10, 2008 is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. Applicant must file a claim set that clearly indicates current status of all the claims. Claims 1-30 (cancelled) ----. Appropriate correction is required.

Response to Arguments

Re 112 1st rejection of claims 31, 41 and 42

3. Applicant's arguments filed November 10, 2008 have been fully considered but they are not persuasive.

Examiner had pointed out in last office action that specification states "It can be assumed that the presence of hCG β7, β6, and β6e is an indicator for an optimal implantation. The lack of hCG β7, β6, and β6e indicates the opposite: the possibility of implantation in this cycle is not to be expected." (see page 16 lines 2-4). Thus specification only **provides an assumption** which forms the basis of the claimed method. **This assumption is not substantiated** by any clinical data.

In response to this querry by Examiner, Applicant did not provide any data but responds by quoting parts of specification on page 12, 3rd full paragraph, that state "It has been recognized that the contents of β6 hCG and β7 hCG in the body's own epithelial tissue or blood cells determines the success of an implantation fundamentally and that therefore the knowledge of the amount of hCG β7 and β6, considered absolute or relative in knowledge of the quotient of hCG β7, β6 as numerator and hCG β5, β8, β3 as denominator provides information in regard to the promising moment of implantation."

What Examiner is asking the Applicant is to either divulge the source of scientific information where the data that forms the basis of the above statement can be found or to provide the data that lead the inventors to arrive at this conclusion.

No statistical data is provided that tells one of ordinary skill how tight is this correlation between detection of β7-hCG, β6-hCG, and β6e-hCG mRNA and receptivity of endometrium.

On page 7 Applicant goes on to state "For diagnosing the receptivity of the endometrium, preferably tissue from the endometrium or from the cervical lining or peripheral blood is removed from the female patient and the analysis of the mRNA expression is determined in this blood or tissue sample with the method according to the invention. Based on the level of the determined mRNA expression of β7-hCG and/or β6-hCG and/or eβ6-hCG it is then possible to draw conclusions in regard to the receptivity of the uterine for an embryo in the current or the subsequent cycle." On page 13 (3rd full paragraph) it is stated, after two

paragraphs that explain the procedures used, that "A positive detection of mRNA of β6-hCG, β7-hCG or e β6hCG indicates that the endometrium differentiates in the direction toward implantation readiness." Thus, the inventors have found that type 1- β-hCG (β7, β6, eβ6) is an indicator for successful implantation and have set forth positively in the specification that mRNA expression of β7-hCG and/or β6-hCG and/or eβ6-hCG is an indicator for implantation readiness.

Examiner agrees that specification provides details to the one of ordinary skill how to determine the mRNA expression of the various genes. As pointed out by Applicant the method is novel hence is not supported by any prior art publication therefore Examiner would like one of ordinary skill in the art to be provided a complete disclosure of the data that leads Applicant to make statements like "type 1- β-hCG (β7, β6, eβ6) is an indicator for successful implantation" and "based on the scientific finding ..." (page 11, 3rd to last line; page 12, lines 4/5) that "It has been recognized that the contents of β6 hCG and β7 hCG...". The inventors have recognized and scientifically determined that β7-hCG and/or β6-hCG and/or e β6-hCG indicate by their presence implantation readiness while their absence indicates that implantation is not possible. Once again Examiner wants to see the data based on which inventors came to "recognize that β7-hCG and/or β6-hCG and/or e β6-hCG indicate by their presence implantation readiness while their absence indicates that implantation is not possible".

Further Applicant states "In healthy endometrium expression of hCG (β6, β7, eβ6) during the cycle will increase. At the beginning of the cycle no endometrial ehCG can be detected. In the middle and in the later phase as well as in the pre-decidual phase of the secretory cycle the ehCG can be detected. The middle luteal phase of the cycle, as is well known, is the phase in which the small window of implantation is present in which the woman can become pregnant. The ovulation occurs about day 14. The fertilization can take place in the first 12 hours after ovulation. The window of implantation in which the embryo can implant in the endometrium is between day 20 and day 24 of the cycle. When in the endometrium of the secretory phase of the cycle no hCG can be detected, a natural or artificial fertilization has no chance of success".

Examiner would like to see the data where expression of hCG (β6, β7, eβ6) during the cycle has been followed in patients that allows the Applicant to make the conclusory statements such as "At the beginning of the cycle no endometrial ehCG can be detected. In the middle and in the later phase as well as in the pre-decidual phase of the secretory cycle the ehCG can be detected". These correlations are based on a clinical study of how many females (in other words what was the sample size of the study based on which Applicant has arrived at these conclusions? Examiner has found no such information provided in the specification as filed. How tight was the correlation in the data set studied? were there any false positives?

These are relevant questions the answers to which must be available to one of ordinary skill in the art in order to practice the invention, otherwise on of

ordinary skill who wants to practice the invention would have to perform the clinical trials using appropriate subject populations and monitoring them through out the cycle to determine how tight if any correlation exists between expression of hCG (β6, β7, eβ6) and receptivity for implantation. This would amount to undue experimentation for one of ordinary skill, who wants to practice the invention. Hence 112 1st par. enablement rejection is being maintained.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 31, 41, 42 and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 31, 41, 42 and 62 as currently recited are drawn to a method for determining receptivity of the endometrium for implantation based on detection of at least one β7-hCG, β6-hCG, and β6e-hCG mRNA in the cells from endometrium or menstrual blood. The step c) recites "determining the receptivity as follows:

1. no β7-hCG, β6-hCG, and β6e-hCG is detected: the endometrium is not receptive;

2. at least one of β7-hCG, β6-hCG, and β6e-hCG is detected: the endometrium is receptive for implantation.

Claims 31, 41, 42 and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, teaches detection of β7-hCG, β6-hCG, and β6e-hCG from cells that are endometrial in origin; and teaches detection of β3-hCG, β5-hCG, β8-hCG, β7-hCG and β6-hCG from tumor tissue; but does not reasonably provide enablement for the method for determining receptivity of the endometrium for implantation based on detection of at least one β7-hCG, β6-hCG, and β6e-hCG mRNA in the cells from endometrium or menstrual blood.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 31, 41 and 42 are drawn to a method for determining receptivity of the βhCG mRNAs based on detection of at least one β7-hCG, β6-hCG, and β6e-hCG mRNA in the cells from endometrium or menstrual blood.

The specification recites three embodiments (# 1-3) that are drawn to RT PCR methods of detecting various βhCG mRNAs. Embodiments 1 and 2 are allegedly directed to diagnostic of receptivity of the endometrium for implantation of an embryo, while Embodiment 3 is allegedly dealing with retrospective diagnostic of the receptivity of the endometrium for implantation of an embryo. However, as will be further discussed, there is no support in the specification and prior art that allows one of ordinary skill to conclude that mere detection of one of the βhCG mRNAs recited above in the endometrial cell indicates that endometrium is receptive for implantation.

The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Examiner has carefully looked through the specification and does not see any data that has been provided, which allows one of ordinary skill in the art to determine this correlation between detection of mRNA of any of the above 3 genes and receptivity of endometrium for implantation.

At the very outset specification states "It can be assumed that the presence of hCG β7, β6, and β6e is an indicator for an optimal implantation. The

lack of hCG β7, β6, and β6e indicates the opposite: the possibility of implantation in this cycle is not to be expected." (see page 16 lines 2-4). Thus specification only **provides an assumption** which forms the basis of the claimed method. **This assumption is not substantiated** by any clinical data.

No statistical data is provided that tells one of ordinary skill how tight is this correlation between detection of β7-hCG, β6-hCG, and β6e-hCG mRNA and receptivity of endometrium.

Review of the prior art indicates that having a reliable method of determining receptivity of endometrium for implantation will be of great utility for clinicians working in the field or Assisted Reproductive Technologies, however the state of the art both prior art and even post filing art is still fraught with controversies and unpredictability.

Lindhard et al. (2002) Fertility and Sterility Vol. 78 No 2 pp 221-233 provide a good review of literature on various endometrial factors assumed to be of importance to implantation and to evaluate their potential clinical value in the assessment of endometrial function. They recite a number of cytokines, a specific integrin, glycodelin, and polymorphic mucin— which have all been shown to play important roles in the cascade of events that lead to implantation. This review does not mention any of the hCG markers recited in the instant claims as one of the art recognized molecules which are tested biochemically while evaluating endometrial function at the time of implantation. The reviewer concludes by stating "the usefulness of these factors to assess endometrial receptivity and to estimate the prognosis for pregnancy in natural and artificial

cycles remains to be proven" (See abstract). This leads Examiner to the conclusion that the level of unpredictability in the art regarding assessment of endometrial receptivity based on use of molecular markers is high.

Acosta et al (2000) (provided to applicant previously by Examiner) had designed a prospective clinical study to determine the window of implantation in healthy fertile women. Acosta et al. like the previous reviewer does not mention use of hCG marker as one of the markers that are used for endometrial dating. In this review of endometrial dating Acosta et al. conclude that three most cited markers that frame the window of implantation do not correlate in their study (see abstract).

Thus both Lindhard et al. and Acosta et al. teach that at the time of filing the prior art does not seem to recognize βhCG as a molecular marker that can play any role in determining the receptivity of endometrium. Hence the usefulness of these 3 (βhCGs) factors to assess endometrial receptivity and to estimate the prognosis for pregnancy in natural and artificial cycles remains to be proven.

Licht et al. (2003) Fertility and Sterility Vol. 79 supple 1 pages 718-723 investigated whether human endometrium does express full-length hCG/LH-receptor mRNA and whether this mRNA-expression is regulated in a cycle dependent way in endometrium specimens derived from various phases of the menstrual cycle (see page 718 last par). Their study shows there is cycle - dependent regulation of hCG/LH receptor mRNA by changes in the alternative

splicing pattern and down regulation of full length hCG/LH receptor mRNA in early decidua. (see abstract).

Fazlebas et al. (1999) Proc. Natl. Acad Sci USA vol. 96 pp 2543-2548 teach modulation of the baboon uterine endometrium by chorionic gonadotrophin during the period of uterine receptivity. They teach presence of luteinizing hormone (LH)/CG receptors and associated G proteins has been documented in the human endometrium, In addition, human CG (hCG) and the α-subunit of hCG have been shown to induce decidualization of human stromal fibroblasts in vitro. (see page 2543 par. 3).

Based on studies of Licht et al and Fazlebas et al., it is clear that hCG hormone acts on endometrium. They conclude "This study demonstrates that CG has physiological effects in vivo on the primate uterine endometrium during the period of uterine receptivity" (see page 2546 par. 1). So there is no doubt that exogenous hCG levels influence endometrium receptivity and implantation. The hCG receptor binds hCG that is present in the blood and however art does not give any indication that mere detection of mRNA coding for any one of β7-hCG, β6-hCG, and β6e-hCG subunits produced endogenously in the endometrial cells can be correlated to receptivity of endometrium for implantation.

Post filing art Coutifaris et al. (2004) Fertility and Sterility vol. 82 No 5 Nov 2004 pp 1264-1272 reflects the lack of consensus among the researchers in the field of Fertility and Sterility regarding molecular markers that might be useful for monitoring endometrial development. In the article entitled "Controversy: Endometrial Biopsy and Infertility Status? Coutifaris et al. conclude histological

dating of timed endometrial biopsy is not related to fertility status (see title) and state" in conclusion, the timed endometrial biopsy by histological dating of the endometrium provides no clinically useful information as screening test.---- continued research on the emerging molecular markers of endometrial development should be encouraged" (see page 1271 last par).

What none of the articles even post filing suggest is that 1) β7-hCG, β6-hCG, or β6e-hCG can be used as molecular marker to determine endometrial receptivity and 2) that there is any correlation between the endogenous expression of at least one β7-hCG, β6-hCG, or β6e-hCG mRNA and endometrial receptivity.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large because art uses a number of different criteria for establishing the stage of development of endometrium. As described above, so far no one in the art has studied whether any correlation exists between expression of any one of the β7-hCG, β6-hCG, or β6e-hCG mRNA and endometrial receptivity. Before the claimed method can be used by one of ordinary skill, appropriately designed controlled clinical trials would have to be conducted so that one of ordinary skill knows that mere detection of at least one β7-hCG, β6-hCG, or β6e-hCG mRNA is an indicator of receptivity of endometrium for implantation.

If the data indicates that such a correlation exists then conditions would be have to be determined that would enable one of ordinary skill to make the diagnostic or prognostic assessment.

Working Examples

The specification as filed has no working examples of the actual number of patients that were studied and the results obtained that allows one to come to the conclusion. One prophetic example that is provided at the end of specification is not sufficient to provide support for the claim that mere expression and detection of at least one of β7-hCG, β6-hCG, and β6e-hCG mRNA from cells of endometrium is an indication that the endometrium is receptive.

Guidance in the Specification.

Other than an assumption, the specification provides no scientific evidence to support the correlation that forms the basis of the disclosed method to determine receptivity of endomterium for implantation in humans.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in an area of Fertility and Sterility where medical community has not yet reached a consensus on molecular markers that best determine the receptivity of endometrium for implantation, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to

answer the fundamental question which is: can mere detection of one of the three mRNAs recited be used as a sole and sufficient molecular marker that indicates endometrium is receptive for implantation? Thus given the nature of claims in an art whose nature is identified as unpredictable, the controversy in the field re markers that can be used to determine receptivity of endometrium, the unpredictability of that art, the large quantity of research required to define these unpredictable variables in humans, the lack of guidance provided in the specification, the absence of a working example and no suggestion or indication in the prior art that the recited markers can be used a molecular markers balanced only against the high skill level in the art, it is the position of the Examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as recited.

Conclusion

6. All claims under consideration 31, 41, 42 and 62 are rejected.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1637

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